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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/365,349	07/30/1999	NORMAN TERRY	B99-085	1676

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EXAMINER	
IBRAHIM, MEDINA AHMED	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/365,349	TERRY ET AL.	
	Examiner	Art Unit	
	Medina A. Ibrahim	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's response filed 03/28/05 in reply to the Office action of 12/22/04 has been entered. The manuscript titled "Expression of High-Affinity Sulfate Transporter in Brassica juncea Affects Metal Tolerance and Accumulation" by Lindblom et al (2005) submitted with the response has been considered.

All previous objections and rejections not set forth below have been withdrawn.

Claims 1-24, pending in this application, are considered.

Claim Rejections - 35 USC § 112

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Brassica plant comprising a recombinant glutamylcysteine synthetase (ECS) expression construct and a method for decreasing heavy metal content of a medium containing an excessive amount of a heavy metal trace element by overexpressing a nucleic acid encoding glutamylcyteine synthetase in said Brassica plant, does not reasonably provide enablement for any commercially available variety from the family of Salicaceae, Solanaceae,Caryophyllaceae or Brassicaceae including *Populus angustifolia*, *Nicotiana tabacum* or *Silena cucubalis* plant species which is genetically engineered to overexpress ECS for enhanced heavy metal accumulation, and a method of its use to remove heavy metal from a metal contained media. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention commensurate in scope with these claims. This rejection is repeated for the reasons of record as set forth in the last Office action of 12/22/04. Applicant's arguments filed 03/28/05 have been considered but are not deemed persuasive.

Claims 1, 4, 9-12 and 23-24 have been amended to recite a commercially available variety of Salicaceae, Solanaceae, Caryophyllaceae or Brassicaceae including *Populus angustifolia*, *Nicotiana tabacum* and *Silena cucubalis.* However, the specification does not enable the plant species as broadly claimed and methods of its use.

Applicant argues that the specification offers large number of suitable commercially available varieties and exemplifies *Brassica Juncea, Populus angustifolia, Nicotiana tabacum and Silene cucubalis* overexpressing ECS for enhanced accumulation of heavy metals. Applicant asserts that any suitable plant species can be substituted into the same method (pages 7-8, response). On pages 9-10 of the response applicant cites prior art references that teach unpredictable and uncertain relationship between overexpression of ECS and enhanced heavy metal accumulation.

This is not persuasive because the specification exemplifies Brassica juncea only and a method that employs said plant and the specification does not support the broad scope of the claims drawn to a commercially available variety of Salicaceae, Solanaceae,Caryophyllaceae or Brassicaceae including *Populus angustifolia*, *Nicotiana tabacum* or *Silena cucubalis* and a non-brassica species from Brassicaceae which is genetically engineered to overexpress ECS for enhanced heavy metal accumulation, and a method of its use to remove heavy metal from a metal contained medium.

Although Applicant repeatedly asserts that exemplified plants other than Brassica are disclosed in Table 2 of the specification, there is no data presented in the specification to support the results in the Table. Each recombinant plant received "+++", and each wild type plant received "+/-" designations with no explanation as to what amounts correspond to the designations. Therefore, the enabling disclosure is limited to the transformation of a *Brassica species* with glutamylcysteine synthetase encoding nucleic acid for enhanced heavy metal accumulation and transformed Brassica juncea with enhanced heavy metal accumulating property.

In Genentech Inc v. Novo Nordisk A/S (42 USPQ2d 1001 at p. 1005). The CAFC stated, "(P)atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable....While every aspect of generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention....[w]hen there is no disclosure of any specific starting material or conditions under which a process can be carried out, undue experimentation is required.....". The *Genentech* court also held that [w]hile every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention". Id. In this case, as in *Genentech*, the specification does not provide the "reasonable detail to enable members of the public to understand and carry out the invention".

Furthermore, the Caryophyllaceae family comprises 89 genera and 2, 070 plant species and the Solanaceae family has about 95 genera and at least 2400 plant species. The Brassicaceae family has over 400 non-Brassica genera. Applicant has provided no guidance for how to identify preferred varieties having relatively metal accumulating capacity (see attached search results). Goldsbrough (1999, previously provided) that teaches overexpression of ECS gene did NOT increase the Cd tolerance of wild type Arabidopsis thaliana (a Brassicaceae). De Knecht et al (1992, previously provided) disclose Cd-tolerant Silena vulgaris (a Cryophyllaceae) plants synthesizing LESS phytochelatins than sensitive plants when exposed to the same concentration of Cadmium. From the family of Solanaceae, Chen et al (1994, previously provided) teach that the observed cadmium tolerance in tomato cells which overproduce ECS was not stable over time and that metal-tolerant plants exhibit inferior growth characteristics, and Delhaize et al (1989, previously provided) that teach overproduction of ECS or phytochelatins was not responsible for Cd tolerance in Datura innoxia. Noctor et al (1998) and Arisi et al (1997) both disclose transgenic poplars (of the family Salicaceae) overexpressing ECS with no metal accumulating property. Because the prior art establishes an uncertain and unpredictable relationship between overexpression of glutamylcysteine synthetase and heavy metal accumulation; and because, as discussed above, the specification provides only a single example of a metal accumulating plant, it would require an undue amount of experimentation by one skilled in the art to practice the invention using plants other that Brassica plants without further guidance.

Applicant asserts that the enablement rejection and the resultant Board decision of 07/31/03 rely upon Noctor et al (1998) reference that disclose unpublished preliminary experiment, and argues that Arisi et al (2000) from the same laboratory as Noctor report their completed experiments which show the upregulation of ECS provides enhanced heavy metal accumulation in transgenic poplars (response paragraph bridging pages 6-7).

This is not persuasive because the rejection is based upon a complete analysis of the *In re Wands* factors as outlined in the previous Office actions of 12/22/04 and 04/20/04, and does not rely solely upon Noctor et al. Other cited references, Goldsbrough (1999), De Knecht et al (1992), Chen et al (1994), and Delhaize et al (1989), Hofgen et al(2001), Salt et al (1996), Peer et al (2003), and Guerinot (2001) to also support the unpredictable nature of the claimed invention. Applicant has provided no evidence to the contrary.

With respect to Arisi et al (2000) reference, Applicant is directed to the Response of 03 February 2000, page 2, bottom paragraph, where Applicant stated that Arisi et al (1997) did not teach enhanced heavy metal accumulation in transformed poplars. Applicant also states on pages 10 of the instant of the response (03/22/05) "[T]he prior art establishes an uncertain and unpredictable relationship between ECS expression and heavy metal accumulation, and specifically teaches (in both Noctor et al. and Goldsbrough) that over expression of ECS will not yield heavy metal accumulators." The transformed plants of Arisi et al (1997) and Arisi et al (2000) are identical, i.e., ggs11

and ggs28 lines first disclosed in Arisi et al (1997), page 367, Table 1; and Arisi et al (2000) page 145, Figures 1 and 2.

While Arisi et al (2000) discloses transformed ECS Poplars and non-transformed Poplars with increased Cd accumulation in the leaves, growth was inhibited at the highest soil cadmium concentration in all plants (see at least the Summary on page 143). At the paragraph bridging columns 1 and 2 of page 148, the cited reference states " [O]verexpression of either y-ECS or GS increased Cd accumulation and tolerance in Indian Mustard. In transformed poplars, enhanced tissue y-EC and GSH do NOT confer increased tolerance to Cd in terms of amelioration of growth". Therefore, Arisi et al make explicit comparison between Brassica juncea having enhanced Cd accumulation and tolerance as a result of ECS overexpression and ECS Poplars with no tolerance to the Cd accumulated. It is also noted that Arisi et al (2000), Noctor et al (1998), and Arisi et al (1997), each teach that ECS Poplars which exhibited increased ECS failed either to accumulate Cd or be tolerant to high Cd in the growth medium. The works of Arisi et al (2000), Noctor et al (1998), and Arisi et al (1997) are all from the same laboratory. Therefore, Applicant's arguments in the Appeal Briefs of 08/08/00 and 01/25/01 regarding these references support the instant scope of enablement rejection. Also, Zhu et al (1999) cited by Applicant on page 7 of the response do not support that a plant with inhibited growth is suitable for phytoremediation.

With respect to Applicant's assertion that more experimentation would have been required to produce and evaluate antibodies, which were deemed enabled by Wands, than the instantly claimed method; it is noted that while the production of monoclonal

antibodies which react a particular antigen might have a low success rate, the mechanisms by which said antibodies are produced and function are well understood. The less than 3% success rate may be considered analogous to the rate of recovery of successfully transformed plants following transformation of a population of experimental plants or tissues with a particular gene of interest.

The declaration of Lewis Feldman under 37 CFR 1.132 filed 09/20/04 is insufficient to overcome the rejection of claims 1-24 because the declaration offers opinion evidence rather than factual evidence, as discussed in the last Office action of 12/22/04. Dr. Feldman's declaration provides his expert opinion as to whether one skilled in the art can readily follow practice the two-step method claims and whether one can readily transfer a desired gene into a plant. However, the lack of enablement in the instantly claimed methods lies not with the quantity of experimentation required to practice the two method steps or the plant transformation techniques, but the unpredictability inherent in the behavior and function of that plant, and the ability of a single gene to change the plant 's behavior and function as recited in the claims, and the applicability of said plants in phytoremediation methods. The state of the prior art teaches that the ability of a plant to accumulate heavy metals is a genotype dependent and varies between and within species (Salt et al 1995, previously cited), and that the mechanisms and genetic basis of metal uptake and accumulation in non-Brassica plants are not well understood (Salt et al 1996). The Examiner has provided a number of references that demonstrated the general lack of predictability in the claimed process, both at the time of filing and even later. This unpredictability, taken together with the

claim breadth, the nature of the invention, the limited working examples and the lack of guidance as discussed in the last Office actions of 03/08/04 and 08/26/04, clearly point to undue experimentation as established by *Wands.* The declaration does not provide factual evidence that is contrary to the evidence in record. Therefore, the declaration is not persuasive.

Regarding Lindblom et al (2005), it is noted that the manuscript does not teach ECS gene for metal accumulation or non-brassica transgenic plants for phytoremediation, therefore it does not support Applicant's position.

For all the reasons discussed above and in the last Office actions of 12/22/04 and 04/20/04, the claimed invention is not enabled throughout the broad scope. Therefore, the rejection is maintained.

Remarks

The claims are deemed free of the prior art because the prior art does not teach or fairly suggest a plant that is genetically engineered to overexpress glutamylcysteine synthetase (ECS) for enhanced heavy metal accumulation, nor does the prior art teach a method that employs said plant for heavy metal removal from a metal containing media, as stated in the last Office actions.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Medina A. Ibrahim whose telephone number is (571) 272-0797. The Examiner can normally be reached Monday -Thursday from 8:00AM to 5:30PM and every other Friday from 9:00AM to 5:00 PM. Before and after final responses should be directed to fax nos. (703) 872-9306 and (703) 872-9307, respectively.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Amy Nelson, can be reached at (571) 272-0804.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Mai
6/6/05

MEDINA A. IBRAHIM
PATENT EXAMINER

Medina A. Ibrahim
6/12/05